# Representativeness of Systemic Sclerosis Patients in Interventional Randomized Trials: an analysis of the EUSTAR database

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Abstract: OBJECTIVE: To estimate the extent of and the reasons for ineligibility in randomized controlled trials (RCTs) of systemic sclerosis (SSc) patients included in the EUSTAR database, and to determine the association between patient's features and generalizability of study results. METHODS: We searched Clinicaltrials.gov for all records on interventional SSc-RCTs registered from January 2013 to January 2018. Two reviewers selected studies, and information on the main trial features were retrieved. Data from 8046 patients having a visit in the EUSTAR database since 2013 were used to check patient's eligibility. The proportion of potentially eligible patients per trial, and the risk factors for ineligibility were analyzed. Complete-, worst- and best-case analyses were performed. RESULTS: Of the 37 RCTs included, 43% were conducted in Europe, 35% were industry-funded, and 87% investigated pharmacological treatments. Ninety-one percent of 8046 patients included could have participated in at least one RCT. In complete-case analysis, the median [range] proportion of eligible patients having the main organ complication targeted by each study was 60% [10-100] in the overall sample of trials, ranging from 50% [32-79] for trials on skin fibrosis to 90% [34-77] for those targeting Raynaud's phenomenon. Among the criteria checked, treatment- and safety-related but not demographic were the main barriers to patient's recruitment. Older age, absence of Raynaud's phenomenon, and lower mRSS were independently associated with the failure to fulfill criteria for any of the included studies. CONCLUSIONS: Patient's representativeness in SSc-RCTs is highly variable and is driven more by treatment- and safety-related rather than demographic criteria.

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# Representativeness of Systemic Sclerosis Patients in Interventional Randomized Trials: an analysis of the EUSTAR database.

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**Key messages**

- A poor representativeness of real-life patients in clinical trials is a major factor limiting the generalizability of study results.
- Patient's representativeness in SSc-RCTs is highly variable across studies.
- Older age, absence of Raynaud's phenomenon, and lower mRSS are risk factors for SSc-RCTs inelegibility.

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## Abstract

**Objective.** To estimate the extent of and the reasons for ineligibility in randomized controlled trials (RCTs) of systemic sclerosis (SSc) patients included in the EUSTAR database, and to determine the association between patient's features and generalizability of study results.

**Methods.** We searched Clinicaltrials.gov for all records on interventional SSc-RCTs registered from January 2013 to January 2018. Two reviewers selected studies, and information on the main trial features were retrieved. Data from 8046 patients having a visit in the EUSTAR database since 2013 were used to check patient's eligibility. The proportion of potentially eligible patients per trial, and the risk factors for ineligibility were analyzed. Complete-, worst- and best-case analyses were performed.

**Results.** Of the 37 RCTs included, 43% were conducted in Europe, 35% were industry-funded, and 87% investigated pharmacological treatments. Ninety-one percent of 8046 patients included could have participated in at least one RCT. In complete-case analysis, the median [range] proportion of eligible patients having the main organ complication targeted by each study was 60% [10-100] in the overall sample of trials, ranging from 50% [32-79] for trials on skin fibrosis to 90% [34-77] for those targeting Raynaud's phenomenon. Among the criteria checked, treatment- and safety-related but not demographic were the main barriers to patient's recruitment. Older age, absence of Raynaud's phenomenon, and lower mRSS were independently associated with the failure to fulfill criteria for any of the included studies.

**Conclusions.** Patient's representativeness in SSc-RCTs is highly variable and is driven more by treatment- and safety-related rather than demographic criteria.

## Introduction

Systemic sclerosis (SSc) is a rare, systemic autoimmune disease characterized by vasculopathy, dysregulation of the immune system and fibrosis (1). Due to the rarity of the disease, the heterogeneity of clinical phenotypes (2), and the difficulty to develop reliable outcome measures, conducting research in SSc is challenging (3,4).

Randomized controlled trials (RCTs) are the gold standard to estimate the efficacy of medical interventions (5), and are conducted under rigorous conditions. Aside from patient randomization, the assessment of adherence to protocol, the use of validated statistical methods, and the careful choice of eligibility criteria are necessary to minimize the occurrence of bias and to produce reliable results within the sample of individuals participating in the study (internal validity)(6). However, if the recruited subjects are not sufficiently similar in clinically relevant characteristics to those seen in daily practice, the applicability of study results to a target population can be impaired (7,8). This means that individuals underrepresented in trials could be prevented from receiving the benefits of a new drug or, conversely, be exposed to unexpected harms. The extensive use of unnecessary, and too restrictive eligibility criteria, is the main driver of poor generalizability of RCTs results (9). This issue has been shown to be common across different medical specialties, but few data are available for SSc (10). The only study in SSc, published more than 10 years ago (11), found that only a minority of SSc patients could have been suitable to enter in RCTs, but reasons of such low eligibility rate were not investigated. Considering the importance of ensuring the highest number of SSc patients to be potentially enrolled and therefore benefit from interventions investigated in clinical trials, we planned this

study: to estimate to what extent SSc patients enrolled in the EUSTAR database could have participated in RCTs conducted over 5 years; to determine patient's characteristics associated with RCT non-eligibility; and to analyze geographical differences in patient's eligibility.

## Methods

### *Search, data collection and definition of eligibility criteria in registered RCTs*

On 28 February 2018, we searched on Clinicaltrials.gov (12) all records of interventional SSc-RCTs registered from January 2013 through January 2018. We used the terms 'systemic sclerosis' OR 'scleroderma' OR 'SSc'. We defined as interventional a study in which participants are assigned to groups receiving therapeutic intervention/treatment as determined by protocol. We excluded fundamental research, diagnostic and cost-effectiveness studies, and RCTs for which the EUSTAR database lacked the items needed to identify the main condition investigated (e.g. sleep disorders). Two reviewers (MI, MJ) independently checked the studies against the pre-specified criteria and extracted data by using a standardized form. The complete list is in online file. For both tasks, consensus was reached by discussion. A third reviewer was available in case of unresolved disagreement. The following study characteristics were collected: country, funding, phase of development, planned sample size, type of intervention, type of comparator (placebo, active intervention, usual care, or no intervention). A study was considered being industry-funded if the sponsor, as defined in the glossary of ClinicalTrials.gov (12), was industry. Eligibility criteria were extracted for each study. Exclusion criteria were reformulated to obtain the correspondent inclusion criteria. For example, a criterion excluding patients with a serum creatinine >2.0 mg/dl, was rephrased in an equivalent criterion including patients with a creatinine ≤2.0 mg/dl. Then, each criterion was classified in one of the

following categories: *characteristics of the disease*: defining clinical parameters of the disease being studied; *treatment:* concerning future, previous or current drug intake, or surgery; *safety:* organ function, laboratory test and co-morbidity requests that ensure the safety of the participants to enter the trial; *demographic criteria*: related to age, sex, ethnicity; *ethical and administrative*: attempting to ensure conformity with legal and ethical norms of human experimentation and functioning of the study (9). Trials were grouped according to the SSc organ manifestation investigated (skin fibrosis, interstitial lung disease [ILD], digital ulcers, Raynaud's phenomenon (RP), gastrointestinal tract, pulmonary hypertension, kidney) (13). Creatinine clearance was obtained from serum creatinine values by Cockcroft-Gault formula (14).

***Data analysis: description of EUSTAR database and trial eligibility assessment in target population***

The structure of the EUSTAR database and minimum essential dataset have been described previously (15, 16). Local ethic committee permission for each EUSTAR center, and patient written informed consent were obtained prior to EUSTAR enrolment, as required according to national law(approval from the CCER – Commission cantonale d'étique de la recherche - number 09/022 for Geneva University Hospitals). Trial eligibility was checked for SSc patients having at least one visit in database since 2013. We restricted the study to patient's visits recorded after 2013 to evaluate representativeness in the same time span trials would have been potentially conducted. Number of eligibility criteria with no information in EUSTAR within each category (e.g. ethics) were collected, reported for each study, and considered to be always fulfilled. Criteria requiring the discontinuation of one or more drugs or having a stable dose before enrolment, were also considered always fulfilled. For each trial, we calculated the proportion of potentially eligible patients (i.e. fulfilling

all criteria at each given visit after 2013) for those with no missing data (complete-case analysis). We then adjusted for missing data by performing a sensitivity analysis imputing criterion as not fulfilled (worst-case scenario) or fulfilled (best-case scenario). We then conducted subgroup analyses to identify the rate of (in)eligibility a) among those fulfilling for each trial the 'disease characteristics' criteria (e.g., patients with digital ulcers for trials on digital ulcers), to provide an estimate of representativeness in the sample of patients to whom the intervention would have been delivered; and b) only in countries enrolling at least 100 patients.

Reasons for ineligibility were reported. The main features of patients who resulted to be always ineligible ('never eligible') in overall sample of studies and within each category of trial vs. those eligible in at least one RCT ('ever eligible') were compared.

## Data analysis

Analyses were performed using R 3.3.2. statistical software (R Development Core Team, Vienna, Austria). For categorical variables, data were presented as frequencies and percentages. Continuous variables were expressed as median [interquartile range]. Factors associated with trial ineligibility in all studies, and in subgroups of RCTs grouping more than 3 studies (skin fibrosis, ILD, RP) were identified by univariable and multivariable logistic regression model.

## Results

### Characteristics of patients enrolled in EUSTAR database

In total, 8046 patients, 1193 (15%) males, 31% dcSSc, with a median age and disease duration from the onset of first non-Raynaud's symptom of 58 (IQR 48-67) years, and

9 (IQR 4-15) years respectively, were studied. Main characteristics of patients at first available visit are summarized in Table 1.

***General characteristics of trials***

Among the 37 RCTs included (figure S1 in online file), 43% were conducted in Europe, 35% were industry-funded, 86% investigated pharmacological treatments, with placebo as comparator in most of them (78%). Most RCTs evaluated treatments given for skin fibrosis or RP/digital ulcers. Table 2 shows the main features of the included studies.

Overall, we retrieved from Clinicaltrials.gov 575 eligibility criteria, distributed in the following categories: 46% safety; 29% characteristics of disease; 14% treatment; 7% ethical and administrative; 4% demographic. With the data available in EUSTAR database, we were able to check the fulfilment of 100% of demographic criteria (n=24/24); 90% of disease characteristics criteria (n=154/170); 58% of treatment-related criteria (n=47/81); 26% (n=68/262) of safety-related; and no ethics or administrative criteria.

**Estimation of eligibility**

The proportion of patients who could have entered in at least one RCT was 91% (n=7323) for all studies; 33% (n=2697), 24% (n=1933), 85% (n=6807), and 19% (n=1540) in the subgroups of studies on skin fibrosis, ILD, RP, and digital ulcers, respectively.

The median proportion of eligible patients per trial (in overall and within each trial category) varied greatly, being 11% [0.2-92] for the overall sample of studies; 7% [0.2-62] for all the studies on skin fibrosis, 17% [11- 62] for studies on skin fibrosis recruiting

both lcSSc and dcSSc (n=4), 4% [0.2-11] for those including only dcSSc (n=11); 10% [1.5-42] for studies on ILD (n=5); 48% [14-92] for studies on RP (n=7); and 21% [2-24] for those on digital ulcers (n=3) (complete-case analysis) (Table 3). When we restricted the analysis to patients with the condition targeted by the trial, the median [range] proportion of eligible patients increased to 60% [10-100] in the overall sample of trials, ranging from 50% [32-79] for trials on skin fibrosis to 89% [34-77] for those targeting RP (complete-case analysis). The estimates of eligibility per trial in complete-, worst- and best-case analysis, are reported in Table 3.

**Barriers to recruitment and patient's characteristics associated with lack of eligibility**

The analysis restricted to patients with the condition of interest for each study showed that demographic criteria were satisfied by >95% of patients in 87% of studies, while the fulfilment of treatment- and safety-related (>95% of patients in 48% and 53% of RCTs, respectively) criteria was lower.

Comparisons of main features of 'never' vs. 'ever' eligible patients in the whole sample or within each category of studies are provided in online file (complete-case).

Table 4 shows the main patient's demographic and disease-related features associated with the status of 'never eligible', in the whole sample and within each trial category considered (see also Tables S1-S5 in online file). The proportion of 'never eligible' patients was quite homogeneous across centers according to their academic status (Figure S2), and their size (with a higher variability among those recruiting less than 100 patients) (Figure S3). Patients recruited by Internal Medicine centers were more often eligible for none of the RCT compared to other recruiting specialties centers (Figure S4).

Older patients, with a lower modified Rodnan skin score (mRSS), and with no current RP had the lowest chance to be recruited in any of the trials included in the analysis. For RCTs on skin fibrosis, main patient's characteristics independently associated with the lack of criteria fulfilment were older age, longer disease duration, lcSSc subset, low mRSS, and the co-existence of pulmonary hypertension. For RCTs on ILD, older age, creatine kinase elevation and anti-centromere antibodies positivity increased the risk of ineligibility. Anti-Scl-70 positive patients were more likely to be eligible in studies on skin fibrosis and ILD (Table 4).

**Geographical differences in patient's eligibility**

Trial ineligibility was heterogeneous across countries (Figure 1 and Table 5). For RP studies, the rates of 'never eligible' patients were very low in some countries, like UK (1.4%), Hungary (1.4%), and Russia (3.5%), with the highest figure in Croatia (44.8%). Apart from a few exceptions (Denmark, Israel, Romania, Russia), the proportion of 'never eligible' patients for trials on digital ulcers was homogeneously above the 75%. More heterogeneous was the proportion of patients across countries who could have never entered in skin fibrosis (from 40% in Romania to 86% in Denmark), or ILD (from 27% in Russia to 96% in Israel) trials. No difference in never eligibility rates was found among those countries for which a definition of Welfare regimen was available (17)(details in online file, Figure S5).

**Discussion**

We aimed to estimate the extent of and the reasons for ineligibility in RCTs enrolling SSc patients over a 5-year period, and to determine factors associated with trial generalizability of study results.

We have found that the representativeness of real-world SSc patients in RCTs is highly variable across studies, and is driven more by treatment- and safety-related rather than demographic criteria, within those available in the database. The extent to which SSc patients could have entered trials varied according to how patient's representativeness has been estimated, and to the different complications addressed by the studies. Globally, in a first analysis conducted on the overall sample, one of ten patients resulted to be eligible on average in each study, with figures different according to the organ manifestations assessed by the trials. We found, for example, that about half and less than one tenth of patients could have been recruited in studies on RP or in those on skin fibrosis or ILD, respectively. This finding, undoubtedly influenced by the different prevalence of each SSc organ manifestation, is quite similar to that detected by the only paper on the topic conducted more than 10 years ago, and can erroneously lead to conclude that the representativeness of SSc patients in RCTs is very poor (11). In fact, in their paper Villela et al emphasized the very high rate of patients deemed RCT ineligible, with the subsequent issues of poor generalizability of study results (11). To overcome the limitation of such approach, we have also estimated the theoretical eligibility rate within the subgroup of patients for whom interventions were intended to be potentially delivered, i.e. the eligibility of patients with digital ulcers for trials targeting this condition. In this second analysis, the median proportion of patients suitable to fulfill criteria for trials was higher (about 60%) as expected, with still some differences observed among the different trial groups, ranging from 50% in studies targeting the skin fibrosis to about 90% for those on RP. This observation firstly mitigates the concern about a very poor generalizability of SSc-RCTs (11), but also underlines that, even 'adjusting' for the condition of interest, the representativeness of patients in SSc-RCTs even in our optimistic estimate is not 'perfect' yet. Second, the observed lower

inclusiveness in RCTs on skin fibrosis and ILD if compared to that recorded in digital ulcers or RP, would suggest that more stringent criteria, notably treatment- or safety-related, regulate the access in the former group of studies. We can hypothesize that this could represent the obvious consequence of the higher potential safety concerns associated with the use of drugs given for these indications (mostly immunomodulatory drugs), versus those conceived for RP or digital ulcers (mostly vasodilators) (15).

However, whether having a 'perfect' patient's representativeness in RCTs is a realistic and feasible objective, and what should be the ideal cut-off to achieve to consider a study 'representative enough' of patients seen in routine care, is hard to state. In fact, also in daily practice, we choose not to deliver a given treatment for various reasons, such as the absence of an active disease (as patient enrichment in RCTs), or for the co-existence of comorbidities which contraindicate its use or to avoid dangerous drug interactions.

Therefore, establishing if and to what extent the choice of each exclusion criterion could have been reasonably justified on a clinical basis, or conversely mirrors the exaggerated need to minimize the occurrence of drop outs or adverse events, represents a difficult challenge.

The availability of an international database and a large set of eligibility criteria has also allowed us to better depict the features of patients less likely to enter in trials and therefore excluded from the potential benefit coming from the interventions tested, or more exposed to their unwanted harms. On average, older patients, those with a less severe extent of skin fibrosis, and without an active RP fall within this group. The underrepresentation of older patients in SSc-RCTs, even though demographic criteria were not identified as a main barrier to patient's enrolment, suggests that the

combination of factors other than demographic criteria such as comorbidities, exposure to previous treatment, or other safety issues, limit the access to trials to the elderly. Our finding is in line with reports from other specialties (18, 19) and highlights the need to increase the efforts to improve the recruitment also for these more vulnerable and frail patients in our growing older population (20). Post-approval registries can also contribute to fill this gap by helping to evaluate in routine care the risk/benefit ratio of treating the previously unexposed and vulnerable patients (21).

Our data confirms the need to expand the core of studies for patients with lcSSc. We found that lcSSc subset, milder skin involvement, or anti-centromere positivity for studies on ILD, independently impaired the odds to take part in trials and therefore to potentially receive a tested treatment in the real-world. This observed lower inclusiveness of lcSSc patients reflects the numeric imbalance in favor of trials designed for the dcSSc subset. In this regard, it has been recently shown that 25% of RCTs registered between years 2007-2018 were not intended to be delivered to lcSSc patients (3). Furthermore, the paucity of studies addressing frequent and disabling complications seen in this subset of patients like calcinosis, gastroesophageal or intestinal impairment or the physical and facial consequences of SSc, further corroborates our observation. The lower number of studies for lcSSc, despite being the more frequent subset, mirrors the difficulties of designing RCTs for these patients. The heterogeneity of the phenotype, the varied course, ranging from a quiescent or slow progressing disease, the absence of validated outcome measures for some organ involvement, are, among others, the main barriers to conduct trials in lcSSc patients. The development of outcome measures for lcSSc patients is the object of an ongoing study (22).

The analysis of the geographical differences in patient's eligibility shows that apart from a few exceptions, the fulfillment of criteria for trials on digital ulcers was quite homogeneous, while more discrepant data were recorded in the other categories. Capturing the real reasons underlying this finding remains a challenge since eligibility was similar across health care systems, size of recruiting centers, and academic status. Some difference was seen between internal medicine centers compared to specialties centers. Nevertheless, as a descriptive analysis, this information is useful to plan recruitment ability and estimate feasibility of clinical trial.

Some study limitations should be acknowledged. Since we imputed as fulfilled unavailable criteria in EUSTAR, our results represent an optimistic estimation of trial eligibility. Moreover, our analysis did not incorporate all the trials registered in the period considered, since we could not include RCTs intended to investigate aspects for which we had no information in the database (e.g. sleep problems). Study conclusions should therefore be interpreted considering this aspect. Furthermore, the identification of the subgroups of patients for whom interventions were planned, was based on the fulfillment of the 'Characteristics of the disease' criteria since there is not a unique definition for each SSc given complication (i.e. many different possible definitions for ILD). This could have further led to an optimistic estimation of patient's eligibility. Limitations of the analysis on geographical differences in patient inclusiveness should also be acknowledged. Potential reasons for this finding include: a real heterogeneity of SSc phenotypes in different geographical areas (23); differences how patients are recruited in centers/countries; the number of academic versus non-academic recruiting centers in each country.

This paper has several strengths. This study is the first conducted in a large, international sample of real-life patients, allowing more realistic estimates of

(in)eligibility rates by focusing on the subgroups of patients with the peculiar clinical manifestation targeted by the trial. The identification of the main barrier to study participation and the patient's features associated with, represents another novelty aspect and provides knowledge for future study design.

In conclusion, we have shown that the proportion of SSc patients allowed to participate in RCTs is highly variable across studies and that while being aware of the unavailability of certain factors commonly used to enrich cohorts and limiting patient's inclusiveness in trials, treatment-related and general safety issues represent relevant barriers to study participation. Despite the fact that demographic criteria permit the involvement of all patient ages, the elderly are still underrepresented in RCTs. Importantly the need of patients with lcSSc subset is still unmet. A better understanding and awareness of barriers to patient recruitment when designing SSc-RCTs may improve generalizability of results and favour the translation of RCTs efficacy results to real-world patients.

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**Data availability statement.** The data that support the findings of this study are available upon reasonable request.

**Author contributions.**

**Conception and design.** Iudici, Courvoisier. **Acquisition of data.** Iudici, Jarlborg, Lauper, Müller-Ladner, Smith, Allanore, Balbir-Gurman, Doria, Airò, Walker, Riccieri, Vonk, Gabrielli, Szücs, Martin, Distler. **Analysis and/or interpretation of data.** Iudici, Jarlborg, Lauper, Müller-Ladner, Smith, Allanore, Balbir-Gurman, Doria, Airò, Walker,

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## Tables

**Table 1**. Characteristics of SSc patients (n=8046) included in the present study.

| Characteristics | n[a] | Overall sample |
|---|---|---|
| Age, median (IQR), years | 8042 | 58 (48-67) |
| Male sex, n, % | 8046 | 1193 (14.8) |
| Body weight, median (IQR), kilograms | 7017 | 64 (56-74) |
| **Disease characteristics** | | |
| dcSSc subset, n, % | 5069 | 1594 (31.4) |
| Disease duration since first non-Raynaud symptom, median (IQR), years | 6952 | 9 (4-15) |
| mRSS, median (IQR) | 8046 | 4 (0-10) |
| Raynaud's phenomenon, n, % | 7715 | 7325 (94.9) |
| Intestinal symptoms, n, % | 7733 | 1916 (24.8) |
| Puffy fingers, current, n, % | 6484 | 2308 (35.6) |
| Current digital ulcers, n, % | 6027 | 883 (14.6) |
| Pulmonary hypertension by echocardiography, n, % | 7732 | 889 (11.5) |
| DLCO/SB, median (IQR), % of predicted | 5877 | 69 (55-82) |
| FVC, median (IQR), % of predicted | 6188 | 97 (81-111) |
| Renal crisis, ever, n, % | 7974 | 122 (1.5) |
| **Laboratory parameters** | | |
| Creatine-kinase elevation (>3 ULN), n, % | 6500 | 494 (7.6) |
| Anti-centromere positive, n, % | 6747 | 2842 (42.1) |
| Anti-topoisomerase I positive, n, % | 6808 | 2248 (33.0) |
| Anti-RNA polymerase III, n, % | 4560 | 205 (4.5) |

[a] Number of patients with available information for each variable. **IQR,** interquartile range; **mRSS,** modified Rodnan skin score; **SD,** standard deviation; **PAPsys,** systolic pulmonary artery pressure as estimated by echocardiography; **DLCO/sb,** Single breath diffusing capacity for carbon monoxide; **FVC,** forced vital capacity; **ULN**, upper limit of normal.

**Table 2**. Characteristics of RCTs included in the analysis.

| Item and subcategory | RCTs N=37 |
|---|---|
| **International** | 12 (32) |
| **Location of studies*** | |
| North America | 19 (51) |
| Europe | 16 (43) |
| Asia | 13 (35) |
| South America | 6 (16) |
| Oceania | 3 (8) |
| Africa | 2 (5) |
| **Industry-funded** | 13 (35) |
| **Type of intervention** | |
| Pharmacologic | 32 (86.5) |
| Non-pharmacologic | 5 (13.5) |
| **Study design** | |
| Parallel group | 36 (97) |
| Crossover | 1 (3) |
| **Type of comparator** | |
| Placebo | 28 (76) |
| Active (pharmacologic) | 5 (14) |
| Usual care | 2 (5) |
| No intervention | 2 (5) |
| **Eligibility criteria** | N=575 |
| Mean (SD) number of eligibility criteria per trial | |
| Demographics | 24 (4) |
| Characteristics of disease | 170 (29) |
| Ethical and administrative | 38 (7) |
| Treatment | 81 (14) |
| Safety | 262 (46) |
| **Organ manifestation being evaluated*** | |
| Skin fibrosis | 15 (40) |
| Raynaud's phenomenon/digital ulcers | 10 (27) |
| Interstitial lung disease | 5 (13) |
| Gastrointestinal disease | 1 (3) |
| Pulmonary hypertension | 1 (3) |
| Renal disease | 1 (3) |
| Calcinosis | 1 (3) |
| Other | 3 (8) |
| **Sample size** | |
| No. of patients planned to be included or included per study (median, IQR) | 60 (32-90) |

*Multiple answers were possible. **IQR**. Interquartile range.

**Table 3.** The proportion of eligible patients per trial from overall sample and from the subgroup of patients with the condition of interest being investigated by each trial.

| | % eligible pts (overall sample) N=8046 complete case [worst-best] | % eligible pts (with the condition of interest) complete case [worst-best] |
|---|---|---|
| **Skin fibrosis** | | |
| NCT02551042* (CSL Behring Sclero XIII) | 62.3 [20.8-82.6] | 67.6 [28.4-88.6] |
| NCT03068234* | 11 [3.0-21.1] | 79.0 [41.8-98.6] |
| NCT03141125* | 20.5 [6.6-31.5] | 33.2 [12-52.1] |
| NCT03365869* | 14 [5.6-39.8] | 32.2 [15.3-80.6] |
| NCT02921971§ | 1.2 [0.3-3.7] | 19.1 [11.8-45.9] |
| NCT02453256§ (focuSSced) | 5.2 [2.1-8.3] | 53.9 [31.8-97.7] |
| NCT02588625§ | 11.1 [5.4-31.7] | 82.6 [72.7-84.7] |
| NCT02283762§ | 1.6 [0.4-4.5] | 48.4 [33.3-100] |
| NCT02503644§ (FASST) | 8.0 [0-8.0] | 50 [0.8-92] |
| NCT02161406§ (ASSET) | 2 [0.5-4.2] | 25.9 [16-49.6] |
| NCT01785056§ | 7.5 [6.2-10.6] | 56.9 [54.4-77.8] |
| NCT02349009§ | 0.2 [0-5.1] | 20 [11.1-61.1] |
| NCT03274076§° (TOFA-SSc) | 3.3 [0.8-6.9] | 28.3 [17.4-57.4] |
| NCT01651143§° | 4.5 [1.8-7.5] | 59.5 [42.1-98.2] |
| NCT03398837^ (RESOLVE-1) | 11.0 [7.8-36.4] | 95.0 [50.6-97.3] |
| All skin fibrosis, median (IQR) | 7.5 (2-11) | 50 (28.3-67.6) |
| **Interstitial lung disease** | | |
| NCT01862926 (RECITAL) | 30.0 [20.2-53.0] | 76.9 [35.8-95.1] |
| NCT02370693 | 1.5 [0.6-49.6] | 50 [30.1-98.1] |
| NCT02896205 (MYILD) | 42.3 [9.3-81.1] | 68.2 [17.9-96.9] |
| NCT02597933 | 10.5 [0-13.2] | 33.3 [0.8-38.6] |
| NCT01933334 (LOTUSS) | 7.5 [1.2-12.0] | 72.9 [25.5-99.5] |

| | | |
|---|---|---|
| All ILD, median (IQR) | 10.5 (4.5-36.1) | 68.2 (41.6-74.9) |
| **Raynaud's phenomenon** | | |
| NCT03027674 | 48.3 [46.7-59.2] | 49 [47.8-59.9] |
| NCT01090492 | 65.8 [21.6-84.8] | 74.2 [25.3-96.0] |
| NCT03058887 | 18.9 [3.1-48.4] | 54.4 [21.4-91.0] |
| NCT02165111 | 92.0 [48.3-97.5] | 92.9 [49.5-98.8] |
| NCT02480335 | 38.4 [35.5-66.1] | 99.5 [99.5-99.9] |
| NCT02370784 (TAMER) | 13.9 [7.9-26.6] | 100 [0.2-73.2] |
| NCT02260557 | 88.7 [47.1-96.0] | 89.5 [48.2-97.3] |
| All Raynaud's, median (IQR) | 48.3 (18.9-88.7) | 89.5 (54.4-99.5) |
| **Digital ulcers** | | |
| NCT02356809 | 2.4 [0-57.7] | 10 [0.1-92.1] |
| NCT02801305 | 20.6 [16.5-58.4] | 86.4 [86.4-91.8] |
| NCT02733978 | 23.9 [19.1-59.5] | 100 [100-100] |
| All digital ulcers, median (IQR) | 20.6 (2.4-23.9) | 86.4 (10-100) |
| **Pulmonary hypertension** | | |
| NCT03053739 (BosSilSS) | 30.8 [8.3-65.8] | 61.1 [30.3-98.1] |
| **Gastrointestinal** | | |
| NCT02302352 | 44.6 [38.6-51.4] | 100 (100-100) |
| **Renal** | | |
| NCT02047708 (ZEBRA) | 1.1 [0.5-3.3] | 83 [81.5-87.0] |
| **Other** | | |
| NCT01733056 | 7.5 [6.2-10.6] | 56.9 [54.4-77.8] |
| NCT01918904 (STS-CALC) | 6.3 [1.5-50.0] | 30 [29.8-54.8] |
| NCT02780674 | 63.7 [31.5-71.3] | 64 [33.2-72.4] |

***** studies on patients with both lcSSc and dcSSc subset; **§** studies on patients with dcSSc only; **°** Safety as primary outcome, mRss as secondary outcome; **^**study on dcSSc patients having the American College of Rheumatology Combined Response Index score (CRISS) as primary outcome. RCTs. Randomized controlled trials; **IQR**, interquartile range; **ILD**, interstitial lung disease.

**Table 4.** Factors associated with the 'never eligible' status in the whole sample of studies included and according to the disease complication tailored by trials.

| | All trials | | Skin fibrosis | | Interstitial lung disease | | Raynaud's phenomenon | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | Multivariable | Univariable | Multivariable | Univariable | Multivariable | Univariable | Multivariable |
| Factor | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Age | 1.01 (1.00-1.02)* | 1.02 (1.00-1.04)** | 1.03 (1.02-1.03)* | 1.02 (1.01-1.03)** | 1.01 (1.00-1.02)** | 1.01 (1.00-1.02)* | 1.01 (1.00-1.02)** | 1.02 (1.01-1.04)** |
| Male | 0.83 (0.66-1.04) | | 0.54 (0.47-0.61)** | | 0.86 (0.75-0.99)** | | 0.83 (0.69-0.99)** | |
| Time from first non-Raynaud | 0.99 (0.98-1.01) | | 1.07 (1.06-1.08)** | 1.03 (1.02-1.04)** | 1.01 (1.00-1.02)** | | 1.02 (0.99-1.01) | 0.98 (0.96-0.99)* |
| lcSSc | 4.03 (2.92-5.71)** | | 5.41 (4.76-6.17)** | 3.55 (2.59-4.91)** | 1.48 (1.30-1.68)** | | 1.95 (1.59-2.41)** | 2.04 (1.18-2.64)** |
| Raynaud's phenomenon | 0.20 (0.15-0.25)** | 0.30 (0.13-0.80)** | 0.65 (0.51-0.82)** | | 0.53 (0.40-0.70)** | | - | |
| Current digital ulcers | 0.12 (0.06-0.23)** | | 0.69 (0.51-0.93)** | | 0.67 (0.48-0.93)* | | 0.67 (0.48-0.95)** | |
| mRSS | 0.90 (0.89-0.92)** | 0.91 (0.86-0.97)** | 0.93 (0.92-0.94)** | 0.94 (0.92-0.96)** | 0.98 (0.97-0.98)** | | 0.97 (0.96-0.98)** | |
| Creatin kinase elevation | 0.93 (0.64-1.30) | | 0.64 (0.53-0.77)** | | 1.41 (1.13-1.77)* | 2.02 (1.36-3.05)** | 1.01 (0.77-1.31) | |
| Renal crisis | 1.12 (0.58-1.96) | | 0.84 (0.58-1.21) | | 1.22 (0.80-1.93) | | 1.83 (1.18-2.74)* | 3.31 (1.22-8.17)* |
| Dyspnea any stage | 0.90 (0.79-1.02) | | 1.00 (0.94-1.07) | | 0.87 (0.81-0.94)** | | 1.02 (0.93-1.12) | |
| Left ventricular EF | 1.01 (1.00-1.03)* | | 1.00 (0.99-1.01) | | 1.01 (1.00-1.02)** | | 1.01 (1.00-1.02)** | |
| Conduction blocks | 0.95 (0.70-1.26) | | 1.06 (0.91-1.24) | | 0.90 (0.77-1.07) | | 1.13 (0.91-1.39) | |
| Pulmonary hypertension | 1.04 (0.79-1.34) | | 1.99 (1.69-2.34)** | 2.49 (1.69-3.71)** | 1.09 (0.93-1.29) | | 1.41 (1.17-1.70)** | 1.66 (1.02-2.65)° |
| Anti-Scl70 positive | 0.58 (0.47-0.72)** | | 0.44 (0.39-0.48)** | 0.72 (0.53-0.98)* | 0.48 (0.43-0.54)** | 0.56 (0.43-0.74)** | 0.71 (0.61-0.83)** | |
| Anti-centromere positive | 1.68 (1.41-2.01)** | | 2.40 (2.16-2.67)** | | 1.94 (1.73-2.17)** | 1.45 (1.12-1.89)** | 1.44 (1.26-1.66)** | |
| FVC<80% of predicted | 0.72 (0.56-0.92)* | | 0.69 (0.61-0.78)* | | 0.74 (0.65-0.84)** | | 0.92 (0.77-1.10) | |
| DLCO<% of predicted | 0.59 (0.48-0.72)** | | 0.80 (0.71-0.90)* | | 0.80 (0.71-0.91)** | | 0.80 (0.71-0.91)** | |
| Active disease | 0.76 (0.71-0.81)** | | 0.80 (0.78-0.83)** | | 0.90 (0.88-0.93)** | | 0.94 (0.91-0.98)** | |

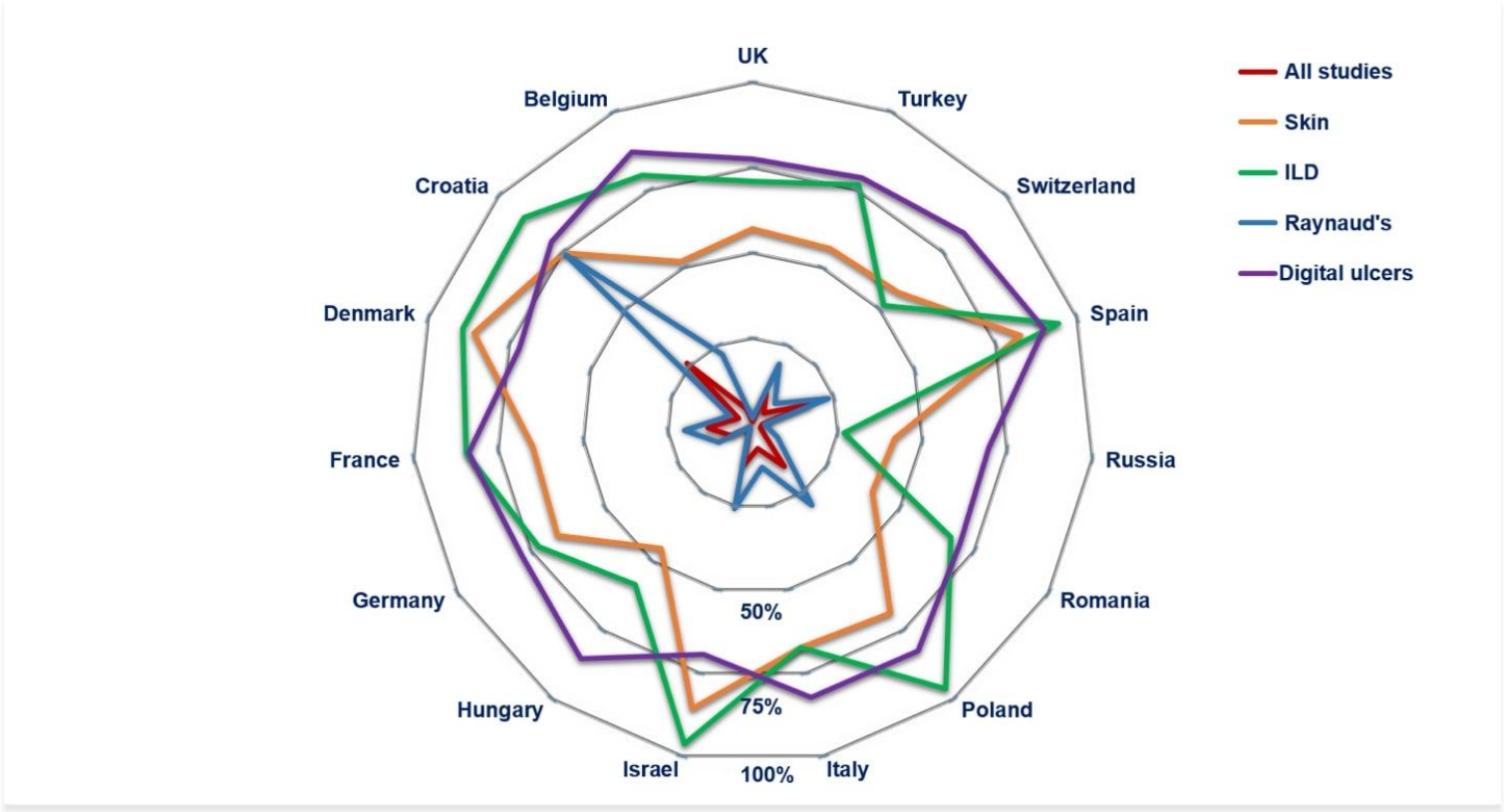
**lcSSc.** limited cutaneous SSc; **mRSS.** Modified Rodnan skin score; **EF.** Ejection fraction; **FVC.** Forced vital capacity; **DLCO.** Diffusing lung capacity for carbon monoxide. **p<0.001, * p<0.05, °0.

**Table 5.** Proportion of 'never eligible' patients according to the country.

| | N of 'never eligible'/total number of patients (%) | | | | |
|---|---|---|---|---|---|
| **Country** | **All studies** | **Skin fibrosis** | **ILD** | **Raynaud's phenomenon** | **Digital ulcers** |
| Belgium | 13/281 (4.6) | 146 (51.9) | 224 (79.7) | 22 (7.8) | 245 (87.2) |
| Croatia | 43/165 (26.1) | 123 (74.5) | 149 (90.3) | 74 (44.8) | 131 (79.4) |
| Denmark | 5/114 (4.4) | 98 (85.9) | 102 (89.4) | 8 (7.0) | 82 (71.9) |
| France | 109/823 (13.2) | 534 (64.9) | 695 (84.4) | 166 (20.2) | 690 (83.8) |
| Germany | 92/1267 (7.3) | 839 (66.2) | 920 (72.6) | 145 (11.4) | 988 (78.0) |
| Hungary | 3/215 (1.4) | 98 (45.5) | 126 (58.6) | 3 (1.4) | 184 (85.6) |
| Israel | 21/167 (12.6) | 143 (85.6) | 261 (96.4) | 43 (25.7) | 116 (69.4) |
| Italy | 153/2031 (7.5) | 1369 (67.4) | 1365 (67.2) | 272 (13.4) | 1671 (82.3) |
| Poland | 22/138 (15.9) | 95 (68.8) | 133 (96.3) | 41 (29.7) | 114 (82.6) |
| Romania | 8/322 (2.5) | 130 (40.4) | 216 (67.1) | 27 (8.4) | 226 (70.2) |
| Russia | 4/141 (2.8) | 59 (41.8) | 38 (26.9) | 5 (3.5) | 98 (69.5) |
| Spain | 108/619 (17.4) | 512 (82.7) | 584 (94.3) | 144 (23.2) | 555 (89.7) |
| Switzerland | 23/545 (4.2) | 313 (57.4) | 281 (51.5) | 47 (8.6) | 454 (83.3) |
| Turkey | 13/132 (9.8) | 74 (56.1) | 101 (76.5) | 25 (18.9) | 104 (78.8) |
| UK | 1/282 (0.35) | 161 (57.1) | 200 (70.9) | 4 (1.4) | 219 (77.6) |

**ILD**. interstitial lung disease.

**Figure 1**. Proportion of 'never eligible' patients across countries for each trial category.




**Legend. ILD,** interstitial lung disease.